

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Monday and Tuesday, November 21 and 22 1983. The President, MICHAEL OLIVER, took the Chair during private business. At the scientific sessions the Chair was taken by A HOLLMAN.

Abstracts of papers

Calcium antagonist for the treatment of heart failure: sustained beneficial effects of felodipine at rest and during exercise.

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Felodipine is a new calcium antagonist with a high degree of vascular selectivity. Its potential value in severe heart failure was examined in acute and chronic oral studies. Acute treatment with felodipine 15 mg in 11 patients increased cardiac index (2.1 ± 0.1 to 3.3 ± 0.2 l/min/m²) and reduced systemic vascular resistance (26 ± 2 to 12 ± 2 units) and left ventricular end diastolic pressure (26 ± 2 to 13 ± 2 mm Hg), $p < 0.001$. Myocardial oxygen supply/demand ratio improved as reflected by increments in coronary flow (141 ± 11 to 176 ± 15 ml/min) and reductions in oxygen consumption (18 ± 2 to 14 ± 2 μ mol/min), $p < 0.05$. A pronounced linear shift in the left ventricular end systolic pressure/dimension relation downwards and to the left confirmed that afterload reduction was the dominant mechanism for these beneficial effects. Chronic treatment with felodipine 30 mg daily in 10 patients improved treadmill exercise tolerance by 24% after 48 hours. Measurements at submaximal exercise showed a fall in pulmonary wedge pressure (22 ± 5 to 13 ± 4 mm Hg) and arteriovenous oxygen difference (12.7 ± 0.9 to 9.4 ± 0.7 vols%) and an increase in stroke index (37 ± 3 to 53 ± 5 ml/beat/m²), $p < 0.001$. Importantly, repeat exercise testing after four weeks showed sustained improvement in haemodynamic indices and exercise tolerance without evidence of tachyphylaxis.

These observations indicate that the selective vasodilator properties of felodipine will extend the clinical application of calcium antagonists to include the treatment of heart failure.

Effects of felodipine on acute haemodynamics and left ventricular function in beta blocked patients with coronary artery disease

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In vitro work suggests that felodipine, a new dihydropyridine vasodilator, has less cardiodepressant action than nifedipine. In a clinical study we showed a negative inotropic effect of nifedipine in a dose that produced a 20% fall in systemic vascular resistance. In this study we measured haemodynamics and plasma concentrations before and 30 minutes after felodipine (0.075 mg/kg orally) in 11 patients with coronary artery disease. To avoid the haemodynamic effects of reflex sympathetic stimulation after vasodilatation, all patients were beta blocked and all measurements and left ventricular angiograms were performed during right atrial pacing at 100 beats/min. At 30 minutes, when a preliminary study had shown that the contrast material (Hexabrix) had no residual effects, felodipine (plasma concentration 17.8 ± 3.6 nmol/l) caused a fall in mean systemic pressure (10.1%, $p < 0.01$) and systemic vascular resistance (30.2%, $p < 0.01$) with an increase in cardiac index (29.6%, $p < 0.01$). There was no significant change in mean pulmonary artery pressure, pulmonary vascular resistance, or left ventricular end diastolic pressure. Left ventricular dP/dt and dP/dt/P were unchanged, while ejection fraction and velocity of circumferential fibre shortening were increased from 49% to 53% and from 1.0 to 1.19 respectively (NS).

Thus felodipine, unlike nifedipine, had no demonstrable depressive effect on left ventricular function, while producing a similar reduction in systemic vascular resistance.

Influences of venous and arteriolar dilatation singly and together in left ventricular failure complicating acute myocardial infarction

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Vasodilating drugs improve left ventricular function, but few studies have examined prospectively the

proportional effects of venous and arteriolar dilatation in the management of acute left ventricular failure after acute myocardial infarction. Accordingly, a randomised between group study of the immediate haemodynamic effects of venodilatation by intravenous isosorbide dinitrate infusion (50–200 $\mu\text{g/kg/h}$) and arteriolar dilatation by intravenous hydralazine bolus (0.15 mg/kg) given either in random sequence (groups 1 and 2, $n=12$) or simultaneously (group 3, $n=6$) was undertaken in 18 males with radiographic and haemodynamic (left ventricular filling pressure >20 mm Hg) left ventricular failure, 6–19 hours after acute myocardial infarction. Control measurements (one hour) preceded either two consecutive 90 min treatment periods (groups 1 and 2) or a single 90 min period (group 3). Given independently both drugs reduced mean systemic arterial pressure (average: -14 mm Hg; $p<0.05$) and vascular resistance ($p<0.05$) whereas only isosorbide dinitrate reduced left ventricular filling pressure (-8 mm Hg; $p<0.01$) and only hydralazine increased cardiac output ($+0.5$ l/min/m²; $p<0.05$) and stroke volume ($p<0.05$) measured by thermal dilution. Isosorbide dinitrate and hydralazine in combination reduced left ventricular filling pressure (-14 mm Hg; $p<0.01$), systolic and diastolic arterial pressure, and total systemic vascular resistance ($p<0.01$). Cardiac output ($+0.6$ l/min/m²; $p<0.01$), stroke volume ($+3$ ml/m²; $p<0.05$), and heart rate ($+9$ beat/min; $p<0.05$) were increased.

In conclusion, combined venous and arteriolar dilatation seems to be of greater haemodynamic benefit than either treatment alone if the fall in mean systemic pressure does not compromise peripheral perfusion.

Captopril in heart failure

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Captopril seems to be useful in the management of heart failure, but few controlled trials exist and its mode of action remains incompletely understood. We treated 14 patients who had severe heart failure with captopril for six weeks before randomisation to two six week periods of replacement with identical placebo or continuing captopril in a double blind crossover study. During the double blind phase on captopril, visual analogue score for dyspnoea fell (34 ± 6 to 16 ± 5 ; $p<0.02$), treadmill exercise time increased (7.6 ± 1.2 to 9.1 ± 1.4 minutes; $p<0.005$), and echocardiographic left ventricular systolic and diastolic dimensions decreased significantly.

Glomerular filtration rate did not change, but renal plasma flow rose (241 ± 21 to 287 ± 28 ml/min; $p<0.05$) and renal vascular resistance fell (21.6 ± 2.1 to 14.9 ± 1.7 dyn s/cm⁵; $p<0.005$). Total body sodium, by in vivo activation analysis, did not change, but serum and total body potassium increased (3.4 ± 0.4 to 3.9 ± 0.4 mmol/l; $p<0.005$ and 2543 ± 135 to 2667 ± 111 mmol; $p<0.05$ respectively). Complex ventricular arrhythmias during ambulatory monitoring, including ventricular couplets (14.3 to $7.6/24$ hours; $p<0.05$) and tachycardia (6.6 to $3.8/24$ hours; $p<0.05$), fell.

Thus in a double blind placebo controlled study, captopril reduced heart size and improved symptoms and exercise capacity. The fall in blood pressure and renal vascular resistance suggests a reduction in systemic vascular resistance, but natriuresis did not occur. The reduction in ventricular arrhythmias could be due to better cardiac function, but potassium state also improved.

Neuroendocrine mechanisms responsible for changes in clinical and haemodynamic state of patients during treatment of chronic heart failure

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The treatment of chronic heart failure often fails to produce long term benefit; clinical improvement may depend on altering fundamental abnormalities of neuroendocrine function. Accordingly, a double blind crossover trial was carried out in 16 patients with chronic heart failure using two agents (captopril and prazosin) with differing neuroendocrine effects to determine whether neuroendocrine changes could explain clinical and haemodynamic responses to treatment. After one month's treatment with each drug given in random order, clinical and haemodynamic improvement occurred with captopril but not prazosin. Captopril increased exercise tolerance ($p<0.05$), and body weight tended to fall; prazosin did not increase exercise tolerance, and body weight increased ($p<0.05$), with oedema developing in six patients. Captopril reduced ventricular filling pressures and systemic vascular resistance and increased cardiac index, both acutely and long term, associated with a reduction in plasma aldosterone ($p<0.05$ in each case). Prazosin reduced ventricular filling pressures acutely ($p<0.05$), but failed to sustain long term any haemodynamic effect; plasma renin activity, aldosterone, and noradrenaline ($p<0.05$) increased with prazosin.

These results suggest that clinical and haemodynamic responses to treatment in chronic heart failure may be the result of changing neuroendocrine mechanisms.

Maintenance of sinus rhythm after elective cardioversion from chronic stable atrial fibrillation: amiodarone compared with quinidine

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A randomised trial has been conducted to determine the efficacy of amiodarone compared with quinidine in maintaining sinus rhythm after elective cardioversion. Eighty one patients (45 male, 36 female; mean age 60 years) with long standing stable symptomatic atrial fibrillation (mean duration 37.8 months) were randomly allocated to receive either amiodarone 600 mg daily (reduced to 200 mg after seven days) (44 patients) or slow release quinidine bisulphate (Kinidin durules) 1500 mg daily (37 patients).

Groups were well matched for age, cardiac diagnosis, duration of atrial fibrillation, heart size, and left atrial size. Significant side effects were more common with quinidine (32.4%) than with amiodarone (5.8%) ($p=0.003$). During the study period 11.4% of patients taking amiodarone and 24.3% taking quinidine were withdrawn because of poor compliance, side effects, or death ($p=0.074$). Patients were reviewed after four days' treatment, when 9.1% (amiodarone) and 18.9% (quinidine) had reverted spontaneously to sinus rhythm ($p=0.076$). The remainder received DC cardioversion, which was unsuccessful in 2% (amiodarone) and 5% (quinidine). Of these, 32.5% (amiodarone) and 13.3% (quinidine) remained in sinus rhythm after one month ($p=0.042$).

We conclude that quinidine may be more effective in restoring sinus rhythm without DC conversion, but that amiodarone was significantly better tolerated and significantly more effective in maintaining sinus rhythm up to one month after DC cardioversion.

Efficacy of oral propafenon in chronic ventricular arrhythmias

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The efficacy of a new class Ic antiarrhythmic drug, propafenon, on ventricular premature contractions during rest and exercise was assessed during a two

phase study: phase 1—an initial two week placebo controlled double blind crossover assessment; phase 2—an open three month follow up. Twelve consecutive patients with symptomatic chronic ventricular arrhythmias resistant to conventional treatment and fulfilling other inclusion criteria underwent an exercise test and were allocated to receive either propafenon or placebo. During the double blind phase propafenon significantly reduced the number of ventricular premature contractions at rest with the patient supine or sitting, during the bicycle ergometer test, and after the exercise test. After three months of treatment a 90–100% reduction of ventricular premature contractions was achieved in 11 patients continuing on 600 to 900 mg of propafenon daily. Treatment was stopped in one patient during the double blind phase because of drug induced left bundle branch block. A prolongation of the PQ and QRS intervals occurred in all patients with propafenon doses exceeding 450 mg/day. Subjective side effects were slight and consisted of taste sensations and minor central nervous symptoms.

These results suggest that propafenon is an effective drug for the treatment of ventricular arrhythmias in selected patients. Atrioventricular or intraventricular conduction disturbances contraindicate its use.

Assessment of a prototype implantable cardioverter (Medtronic 2342) for ventricular tachycardia

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Internal low energy cardioversion via a right ventricular apical electrode has been shown to be successful in terminating ventricular tachycardia. We have assessed the synchronisation of the right ventricular electrogram to the QRS in 12 patients with ventricular tachycardia. We also examined stability and accuracy of sensing of the electrogram using a prototype of an implantable cardioverter (Medtronic 2342, refractory period 205 ms) in 25 episodes of ventricular tachycardia: 14 episodes were right ventricular and 11 left ventricular (RR 105–760 ms, mean 372 ms).

Early sensing of the electrogram (within 45 ms of onset) occurred in 22 episodes (RR 250–670, mean 376 ms), though during these episodes occasional complexes were missed. In one episode (RR 700 ms) sensing, though delayed 80 ms, still fell early in QRS. In another (RR 150 ms) only alternate complexes were sensed with variable delay. In a third (RR 190 ms) a Wenckebach response caused sensing to fall outside QRS. Sensing of the electrogram was equally good for right or left ventricular tachycardia, though in the

latter it occurred later in QRS.

Though sensing from the apex is adequate in ventricular tachycardia arising from either ventricle and will prevent energies being delivered outside QRS, which might induce ventricular fibrillation, rapid tachycardias (RR < 205 ms) may cause malsensing.

Prophylactic antitachycardia pacemaker: permanent pre-excitation

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Advances in dual chamber pacing have enabled us to use a principle first described by Coumel—namely, permanent ventricular pre-excitation—to prevent rather than interrupt re-entry supraventricular tachycardias in four patients with frequent attacks (range three per week to three per day, mean 10 per week) resistant to antiarrhythmic drugs. Initial electrophysiological studies showed orthodromic tachycardias in all patients (two Wolff-Parkinson-White syndrome, two intranodal) with wide initiation zones for atrial extrasystoles (range 40–160 ms, mean range 80 ms). Only one patient had tachycardia initiated by single ventricular extrasystoles. All patients received a Siemens Elema 674 DDD pacemaker programmed to a low standby rate (50 beats/min), highest synchronous rate (160 beats/min), shortest atrial refractory period (250 ms), and shortest atrioventricular delay (7–10 ms).

Repeat electrophysiological studies performed four weeks after implantation showed a reduction in the tachycardia initiation zone to a mean of 20 ms, range 0–60 ms. All patients described a reduction in the incidence of attacks to a mean of two per month, range none to three per month. Two patients noticed breakthrough attacks during exertion due to loss of paced pre-excitation when the highest synchronous rate was exceeded. These attacks were successfully treated with the addition of beta blockade, which should not be necessary when higher synchronous rates become available.

We conclude that programmable dual chamber pacemakers can provide antitachycardia prophylaxis in patients with orthodromic re-entry supraventricular tachycardia.

Endocardial mapping and averaged vectorcardiogram to understand mechanisms of chronic recurrent ventricular tachycardia

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Endocardial catheter mapping was performed during sinus rhythm and ventricular tachycardia at between five and 20 right and left ventricular sites in 40 patients with old myocardial infarction (group 1), four patients with right ventricular dysplasia (group 2), and eight patients with idiopathic ventricular tachycardia (group 3). All ventricular tachycardias were inducible by electrical stimulation. Sixteen group 1, four group 2, and four group 3 patients had an averaged surface vectorcardiogram performed during sinus rhythm to identify the presence of late potentials. Catheter mapping identified late potentials during sinus rhythm in 39/40 group 1, 4/4 group 2, and 0/8 group 3 patients. Averaged vectorcardiogram failed to detect late potentials in 7/16 group 1 patients having late potentials at endocardial mapping. Endocardial late potentials were recorded only in the aneurysm and border zone in group 1 and 2 patients, never outside these areas. Catheter mapping showed continuous electrical activity during ventricular tachycardia in 13/40 group 1, 3/4 group 2, and 0/8 group 3 patients. Continuous activity was recorded only in the aneurysm. Behaviour of continuous activity during spontaneous or induced changes in ventricular tachycardia rate, morphology, or site of origin showed that continuous activity was not necessary to initiate or perpetuate tachycardia. Potentials recorded at the site of origin of ventricular tachycardia were abnormal in groups 1 and 2 but normal in patients in group 3. Recording of areas with late activation during sinus rhythm and during ventricular tachycardia makes re-entry the most likely mechanism of ventricular tachycardia in groups 1 and 2. The mechanism patients of group 3 remains speculative.

Surgical treatment of supraventricular arrhythmias

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Fifty patients have undergone surgery for a variety of supraventricular arrhythmias. Three had atrial tachycardia, nine had paroxysmal atrial fibrillation (three with pre-excitation), two had chronic atrial fibrillation with rapid ventricular rates, and four had atrioventricular nodal re-entrant tachycardia (with a bystander atrioventricular accessory pathway in one). Twenty three patients had atrioventricular re-entrant tachycardia (five with concealed pathways, 18 with the Wolff-Parkinson-White syndrome) and nine had atrioventricular re-entrant tachycardia in addition to pre-excited atrial fibrillation. One had preoperative evidence of two accessory pathways. Twenty nine had arrhythmias refractory to other treatments, 15 were operated on principally because of patient preference,

and six had antiarrhythmic procedures at the time of other heart surgery. In 14 the arrhythmias were considered potentially life threatening.

Cryoablation was used in most patients. Accessory pathway ablation was attempted in all patients with such a pathway. Twenty of 22 left free wall pathways have remained ablated, as have all seven right free wall pathways. One anteroseptal pathway was ablated, but three anteroseptal and four posteroseptal pathways have only had conduction modified. His bundle section was the primary procedure in 14 patients and was successful in 10. There were no operative deaths, but two patients died in the post-operative period. Surgery is a valuable option for the treatment of supraventricular arrhythmias.

Ischaemic heart disease in middle aged British men

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The Regional Heart Study has determined the prevalence of ischaemic heart disease by administered questionnaire and electrocardiography in 7735 men aged 40–59 years drawn from general practices in 24 British towns. The questionnaire included an inquiry into chest pain suggestive of myocardial infarction or angina, knowledge of any diagnosis of heart disease made by a doctor, and details of any regular medical treatment. Overall, one quarter of all men in this study had evidence of ischaemic heart disease on questionnaire or electrocardiogram, or both. A history suggesting myocardial infarction or angina, or both, was present in 14% of the men, with considerable overlap of the two syndromes. Electrocardiographic evidence of ischaemic heart disease was present in 16% of the men (myocardial infarction 4%, myocardial ischaemia 12%). Half of those with histories suggesting myocardial infarction and angina combined had no abnormality in their resting electrocardiogram. Half of those with definite myocardial infarction on electrocardiogram had no history of chest pain at any time. Overall, only one in five of those regarded as showing evidence of ischaemic heart disease in this survey could recall that a diagnosis of ischaemic heart disease had been made by a doctor.

Myocardial infarction and cigarette smoking in a high risk community

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The reasons for the high incidence of ischaemic heart disease in Scotland are not clear. Initiated in 1976, this prospective community study (population 260 000) relates risk factors, coronary arteriographic findings, and reinfarction rate in 145 consecutive patients who were under 45 years of age at the time of proved myocardial infarction. Coronary arteriography was carried out three months after infarction in 116 patients (80%). Multivessel disease (defined as more than one vessel blocked or >50% stenosed) was present in 51%, single vessel disease in 39%, while 10% had normal or insignificantly diseased vessels. Eighty seven per cent of all patients were smokers, with a mean admitted cigarette consumption of 32 cigarettes per day. There was no significant difference in reinfarction rate in the first two months after infarction for non-smokers, smokers, and those who had stopped at the time of first infarction. In the next five years of follow up reinfarction occurred in 19 out of 63 persistent smokers (30%) and in only four out of 56 ex-smokers (7%) ($p < 0.02$, log rank analysis). No reinfarction occurred in 19 ex-smokers who had single vessel disease, while seven out of 18 persistent smokers with multivessel disease reinfarcted ($p < 0.01$). There were 12 reinfarctions in the 53 patients with multivessel disease and four in the 41 patients with single vessel disease ($p = 0.08$). Heavy cigarette smoking is the most prevalent risk factor at the time of initial infarction. Those who stop smoking have a lower reinfarction rate.

Limited influence of knowledge of coronary heart disease risk factors on individual lifestyle

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A total of 1175 subjects from cluster samples in the community completed questionnaires to assess their knowledge of the causes of coronary heart disease and possible preventive measures and to determine individual behaviour related to risk of developing coronary heart disease. In all groups about 50% of subjects identified smoking and diet as causes of coronary heart disease, but fewer than 8% identified smoking, diet, and hypertension. Knowledge of all risk factors was much greater in subjects from higher socioeconomic groups and in younger subjects and schoolchildren than in older subjects and patients with coronary heart disease. Smoking habits were unrelated to knowledge of smoking as a risk factor. Twenty seven per cent of subjects aware of diet as a risk factor had altered their diet appropriately compared with 12% of other subjects. Thirty per cent of those knowing the beneficial effect of exercise took

regular vigorous exercise compared with 17% of other subjects. There is a strong relation between knowledge of the causes of coronary heart disease and social class or educational attainment, but the impact of this knowledge on personal practice is small. Primary prevention trials in the United Kingdom based on risk factor modification by education need to incorporate specific measures to increase the motivation of subjects to alter their lifestyles.

Is there a dose-response effect with beta blocking drugs in secondary prevention after acute myocardial infarction?

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The influence of the dose of beta blocker as a determinant of the outcome during the secondary prevention of myocardial infarction was evaluated by comparing the results of two randomised clinical trials in the same patient population. A total of 723 consecutive male patients aged 35–65 years were randomised double blind to receive either placebo or beta blocking drugs between one and three months after acute myocardial infarction and followed for 12 months. Inclusion criteria were based on World Health Organisation evidence of infarction and exclusion criteria on the usual contraindications to beta blockers. The first group (n=342) were randomised between placebo and oxprenolol 40 mg twice a day; the second group (n=381) between placebo and oxprenolol 160 mg twice a day. The groups were well matched for major pre-entry variables. Treatment was started on average 68 and 31 days after coronary occlusion in the 80 and 320 mg groups respectively. Analysed on an "intention to treat" the cumulative life survival curves for those randomised to placebo were similar (cumulative survival (80 mg) 95.9% *v* (320 mg) 96.0%; *p*=0.77). The cumulative survival curves of the two groups receiving the different doses of beta blocker were significantly different (99.0% (80 mg) *v* 92.4% (160 mg) oxprenolol; *p*<0.001). The numbers withdrawn from active treatment were similar (low dose=50 (25.4%); high dose=47 (25.7%)).

It is unlikely that the different prognoses are explained by the difference in time after myocardial infarction at which oxprenolol was started. These results therefore suggest that the prophylactic benefits of beta blocking drugs after acute myocardial infarction may be dose related.

Validity of ST segment changes as a marker of ischaemia in stable angina

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Holter monitoring in patients with coronary disease has shown episodes of ST depression, with and without angina. Their relation with underlying ischaemia, however, is controversial. We therefore studied 35 patients with stable angina, coronary disease, and positive exercise tests who had symptomatic and asymptomatic ST depression on Holter monitoring. Regional myocardial uptake of rubidium-82 (perfusion) was measured using positron tomography in three circumstances: supine bicycle exercise (81 tests); cold pressor (40 tests); and spontaneous ST depression (14 episodes). Ischaemia was identified if a $\geq 20\%$ reversible inhomogeneity occurred in serial tomograms. ST depression developed in all 81 exercise tests, angina in 79/81, and tomographic evidence of ischaemia in 75/81 (92%). After the cold pressor test, ST depression occurred in 12 patients; only three developed angina, but all 12 showed tomographic defects. All 14 episodes of spontaneous ST depression were accompanied by tomographic defects, but only five by angina. In each patient tomographic defects after the cold pressor test and spontaneous ST depression always occurred in the segment that showed ischaemia after exercise. Episodes of ST depression lasted one to 21 minutes, but tomograms showed disturbances for up to three times longer. In this study, 81/87 (93%) painful and 20/20 (100%) painless ST episodes were accompanied by independent evidence of ischaemia. This suggests that the prolonged and frequently asymptomatic episodes of ST depression seen in Holter monitoring during daily life represent myocardial ischaemia in patients with angina and coronary disease.

Clinical significance of pain free ST depression in coronary artery disease

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To assess the significance of pain free ST depression recorded in patients with angina, 145 Holter tapes from 87 patients with angiographically proved coronary disease were reviewed. Twenty four patients had repeat tapes after coronary surgery, and 10 patients had multiple recordings. The results were compared with patients' diaries, coronary anatomy, and left ventricular function.

In nine of the 10 patients with multiple recordings painful episodes of ST depression were deeper than pain free ones ($p < 0.01$), but this difference was blurred when pooled data from many patients were used. Patients with multiple and prolonged pain free episodes did not differ from the rest with regard to coronary anatomy or left ventricular function. Arrhythmias were seen on 27 tapes, but these usually occurred during painful episodes or were unassociated with ischaemia. In five patients unifocal ventricular extrasystoles were seen during pain free episodes. Pain free episodes were substantially reduced (48%) by successful graft surgery, but to a lesser degree than painful ones (93%).

The proportion of pain free to painful episodes in a given patient depends on how easily the ST changes are projected on to the chest wall. Pain free episodes represent less ischaemia and are not particularly associated with chronic ventricular dysfunction or cardiac arrhythmias.

Diurnal variation of ambulatory ST segment changes in stable exertional angina

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Fifty patients with confirmed exertional angina who showed a minimum of 1.0 mm of horizontal or down-sloping ST segment depression on exercise testing and either positive thallium 201 scintiscans or coronary angiograms were studied. All drugs were withdrawn for a minimum of two weeks before 24 hour ambulatory electrocardiography was performed using a twin channel high fidelity frequency modulated Oxford Mk II tape recorder. Tapes were played back via a Pathfinder analyser and ST segment trend plotter. The number of episodes of ST segment depression and elevation in excess of 0.5 mm which lasted three minutes or more were derived from the trend plot and summated over four hourly blocks. A total of 631 episodes of ST depression were observed in lead CM5 and 523 in lead CC5 over 24 hours compared with 88 and 83 episodes of ST segment elevation. A distinct diurnal variation of ST depression episodes was observed, with the peak frequency occurring between 0800 and 1200 and 1200 and 1600 corresponding to higher average heart rates. ST segment elevation showed a reverse pattern with most episodes occurring between 2400 and 0400 and 0400 and 0800. More than 90% of episodes of ST depression were associated with concomitant rises in heart rate compared with less than 50% of episodes of ST elevation. These observations point to two distinct mechanisms

implicit in the genesis of ST segment change and have important practical therapeutic implications.

Nocturnal angina: the importance of increased myocardial oxygen demand

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Increased myocardial oxygen demand is responsible for effort angina whereas coronary spasm is regarded as causing rest angina. We studied 11 patients, six with day time effort angina and five with effort and nocturnal angina (2400–0600). All had proved coronary artery disease and episodes of ST depression (≥ 1 mm) on ambulatory monitoring. Heart rate and ST changes were measured every 5 s, and the onset of ST depression was timed from the earliest change measured with a magnifying lens. All nocturnal episodes were compared with each patient's most severe painful and painless effort episodes. In all but one of the 37 episodes (16 nocturnal, 21 effort) the heart rate rose before the onset of ST depression. ST depression followed a tachycardia by 65 ± 35 s and 29 ± 26 s during the painful and painless nocturnal episodes respectively. In comparison, ST depression followed the tachycardia by 98 ± 81 s and 71 ± 41 s during the painful and painless effort episodes respectively ($p > 0.05$). During effort episodes the heart rate increased from 74 ± 10 beats/min to 94 ± 13 beats/min and during nocturnal episodes it increased from 68 ± 14 beats/min at rest to 89 ± 10 beats/min before the onset of ST depression. No significant differences existed in these variables between nocturnal and effort, painless or painful episodes.

These results suggest a similar pathophysiological mechanism for production of nocturnal and effort myocardial ischaemia in patients with obstructive coronary disease.

Determinants of long term outlook after aortic valve replacement for chronic aortic regurgitation

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M mode echocardiography was performed in 56 patients undergoing aortic valve replacement for aortic regurgitation in order to compare functional outcome with preoperative and early postoperative left ventricular dimensions and severity of symptoms. No correlation was found between severity of symptoms and either preoperative or final cavity size ($r = 0.024$ and 0.0037 respectively). Eight of 20 patients (40%)

with a systolic dimension <5.0 cm were severely symptomatic, but in 9 of 21 (43%) with a systolic dimension ≥ 5.5 cm symptoms were mild or absent. Seventeen of 32 patients (53%) with an abnormal systolic dimension at two months (mean 5.3 cm) had regained normal dimensions by two years (mean 3.2 cm) accompanied by a similar mean reduction in diastolic dimension (1.7 cm). A return to normal cavity size occurred in all 20 patients whose preoperative systolic dimension was <5.0 cm, 10 of 15 (66%) in the range 5.0–5.4 cm, and 11 of 21 (52%) in the range 5.5–7.9. There was only a weak correlation between preoperative and final systolic dimensions ($r=0.63$). Symptoms correlated poorly with preoperative and eventual cavity size, and early postoperative dimensions were of limited prognostic value since late recovery was common (30%). Patients with a systolic dimension >5.0 cm may be at risk, but cavity size alone should not be used to justify surgery in asymptomatic patients.

Positive ultrasonic detection of valvular regurgitation

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Conventional echocardiography can only suggest the presence of valvular regurgitation. The positive non-invasive detection of blood flow can be obtained from pulsed Doppler ultrasound.

We have studied 130 patients, 61 with aortic regurgitation (37 with associated aortic stenosis), 46 with mitral regurgitation (32 having mixed mitral valve disease), and 23 with tricuspid regurgitation. All preinvasive investigations (catheter haemodynamics and angiography) were performed by the pulsed Doppler technique. The Doppler sample volume site furthest away from the valve where regurgitation could be detected was recorded and graded 1 to 3 (near the valve, mid-chamber, distal chamber). Angiographic assessment was graded mild, moderate, or severe by one of us without knowledge of the Doppler findings. The presence of regurgitation was correctly identified in all except two patients (both with mitral prostheses). There was close agreement with regard to assessment of severity (to within one grade in three) in all except five patients.

We consider pulsed Doppler ultrasound greatly enhances ultrasonic imaging by detecting positively valve regurgitation. The use of selected sample volume sites provides a reliable index of severity of regurgitation.

Intrinsic sympathomimetic activity in beta blockers: the importance of basal heart rate reduction in the treatment of day time and nocturnal angina

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The use of beta blockade in the treatment of rest angina is controversial, and the effects of intrinsic sympathomimetic activity in beta blockers in the treatment of severe angina is unknown. We studied 15 patients with angiographically proved coronary artery disease (seven with nocturnal angina) using angina diaries, exercise testing, and 48 hour ambulatory monitoring for ST segment changes. Atenolol 100 mg daily (without intrinsic sympathomimetic activity) and pindolol 5 mg three times daily (with intrinsic sympathomimetic activity) were given in a double blind randomised study. The day time resting and mean nocturnal (2400–0600) heart rates on atenolol (63 and 59 beats/min respectively) were slower than on pindolol (72 and 68 beats/min respectively) ($p<0.01$). Angina was more common and the duration of exercise to ST segment depression was shorter with pindolol ($p<0.01$). Also day time and nocturnal painful and painless episodes of ST segment depression were more common and their duration longer with pindolol (mean 6.2 episodes of 156 mins/24 hours) compared with atenolol (mean 4.3 episodes of 83 mins/24 hours) ($p<0.01$).

The study shows that intrinsic sympathomimetic activity in a beta blocker may have deleterious effects in the treatment of severe angina and that lowering of the heart rate is of benefit in treating both effort and nocturnal angina.

Paradox of subendocardial myocardial infarction

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The prognosis after subendocardial myocardial infarction, as diagnosed by the absence of Q waves on the electrocardiogram in the presence of sequential ST-T wave changes and raised cardiac enzymes, is a subject of controversy. The purpose of this study was to assess myocardial perfusion and ventricular function in 18 patients with subendocardial myocardial infarction by means of rest and exercise 12 lead electrocardiography, thallium 201 scintigraphy, technetium 99 ventriculography, cross sectional echocardiography, and coronary angiography. The non-invasive assessment in 10 patients showed good left ventricular func-

tion with minor regional wall abnormalities in the distribution of the affected coronary artery. Subsequently one of these patients died, one reinfarcted, two progressed to unstable angina, and three had coronary bypass surgery. The remainder were found to have had complete occlusion of distal coronary vessels. Pronounced regional wall abnormalities were found in eight patients, and these were associated with proximal occlusion of the relevant coronary artery. Reversible myocardial ischaemia was shown by exercise electrocardiography and thallium 201 scintigraphy in nine patients.

It is concluded that all patients with subendocardial myocardial infarction should be comprehensively investigated before discharge from hospital, as many will be found to have a high grade proximal occlusion of a coronary artery subtending normal myocardium.

Reversal of cardiac hypertrophy by drug treatment in spontaneously hypertensive rats

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The treatment of hypertension is based on the hypothesis that a reduction in blood pressure will prevent the cardiovascular complications such as cardiac hypertrophy associated with high blood pressure. The purpose of this investigation was to study the effect of long term drug treatment on hypertension and cardiac hypertrophy in spontaneously hypertensive rats in order to find out whether the cardiac hypertrophy is simply the consequence of increased blood pressure or if some other mechanisms might also be implicated. The drugs (in drinking water or food or both) were given (a) to pregnant spontaneously hypertensive rats and continued to their offspring up to 18 to 60 weeks of age, and (b) to spontaneously hypertensive rats with established hypertension. Systolic blood pressure was measured indirectly by a tail cuff method. Cardiac weights were measured at the end of the treatment periods. Minoxidil, isosorbide dinitrate, toltrinitrate, prazosin, metoprolol, and verapamil inhibited the development of spontaneous hypertension, whereas labetalol accelerated the rise in pressure in developing spontaneously hypertensive rats. Lowering of the blood pressure induced by isosorbide dinitrate, metoprolol, verapamil, and prazosin was associated with a decrease in the ratio of ventricular weight to body weight, but despite their effective control of blood pressure, minoxidil and toltrinitrate did not reduce the ratio of ventricular weight to body weight in spontaneously hypertensive rats. The findings that the control of hypertension was not sufficient to

achieve a reversal of hypertrophy and that the drugs were therefore not all equal in their ability to potentiate such a reversal suggest that cardiac hypertrophy is not directly linked to blood pressure per se and may be determined by other factors.

Impaired left ventricular filling in young diabetic women

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To assess left ventricular function in diabetes mellitus, M mode echocardiograms were obtained from 36 normotensive insulin treated diabetic women, mean age 25 years, and 13 age matched healthy women. Echocardiographic tracings of the septum and posterior wall were digitised and continuous plots made of left ventricular dimension and its rate of change. Left ventricular systolic function was normal in both groups. The diabetics with severe microvascular complications, however, had smaller stroke volumes than the controls. The pattern of left ventricular filling was abnormal in 19 diabetics when the mean value ± 2 SD in the healthy women was taken as the normal range of the indices. The most common abnormality was a prolonged rapid filling period. Its duration correlated with the presence of microvascular complications. The electrocardiographic voltage was lower in the diabetic group.

These studies suggest that minor abnormalities in left ventricular function reflecting stiffness of the myocardium are common in young diabetic women. One possible explanation for altered myocardial properties and a lower electrocardiographic voltage is the accumulation of glycoprotein, lipids, or collagen in the interstitium of the myocardium.

Humoral and cellular immunity in congestive cardiomyopathy

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The role of immunological mechanisms in congestive cardiomyopathy was studied. The humoral aspect was examined using sera and endomyocardial biopsy samples to detect anti-heart antibodies or deposition of antibody in vivo by immunofluorescence techniques. No consistent or specific abnormality was found: the presence of anti-heart antibodies in cardiac disease appears to reflect myocardial damage whatever the cause. Immunofluorescence was shown to be an

insensitive test for anti-heart antibodies. In vivo and in vitro cellular mechanisms were studied to see if patients with congestive cardiomyopathy were able to mount a normal cellular immune response and to test whether type IV hypersensitivity to four different cardiac antigen preparations was present (29 patients with ischaemic heart disease and 18 normal people acted as controls). Twenty seven patients with congestive cardiomyopathy were found to have normal cell mediated responses to common antigens. As a group they did not manifest hypersensitivity to cardiac antigens, but seven of 25 patients tested with antigen prepared from the congestive cardiomyopathic heart of a 16 year old boy with a rapidly progressive and fatal illness (two months) showed hypersensitivity. Five of the seven so identified died during the time of study compared with 11% in the rest of the group, and they were characterised by a rapidly progressive illness (mean 19 months).

Acute myocarditis: comparison of echocardiographic and electrocardiographic findings

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Acute viral myocarditis was diagnosed in 59 patients with flu-like symptoms or gastroenteritis based on serial electrocardiograms showing gradually changing negative T wave inversions not responsive to beta blockade or initial elevations of ST segments replaced later by T wave inversions, or both. The electrocardiographic localisation of myocarditis by T wave alterations was as follows: anterior, leads V1-4, I, II; inferior with apical extension, leads II, III, aVF, V5-6; lateral, leads I, aVL, V5-6; diffuse if in two or all three regions. On the echocardiogram myocarditis caused hypokinetic, akinetic, or dyskinetic regional wall motion patterns in multidirectional M mode, with thin echoes and sharp systolic deflections. The echographic location was defined as anterior if these changes occurred in anteroapical regions, inferior if on inferoposterior or inferoseptal regions, and correspondingly posterolateral or diffuse. The localisation of electrocardiographic and echocardiographic changes concurred in 45 patients (75.4%): 10 anterior, 16 inferior, five lateral, and 16 diffuse localisations. Diffuse echocardiographic changes were electrocardiographically rather localised in four patients with anterior and in three with inferior T wave inversions and in only five localisations differed.

Thus acute myocarditis often causes local echocardiographic and electrocardiographic findings which

have similar regional distribution. The sensitive detection in asynergy is helpful in the assessment of carditis.

Effect of acetylsalicylic acid and dipyridamole on the platelet vessel wall interaction in experimental long term vein grafts

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The effect of autogenous vein grafts on platelet function was assessed in the rabbit over a period of eight postoperative months. Activation of platelets, as measured by aggregometry, was detected at one week ($p < 0.005$, $n = 14$) and at one and two months after operation ($p < 0.005$, $n = 11$ and $p < 0.05$, $n = 15$ respectively) but not at four, six, and eight months ($p > 0.05$). Autoradiography after indium 111 labelling showed platelet deposition on 5/5 vein grafts at one week, 7/8 grafts at one month, but on only 1/6 grafts at four and eight postoperative months. Treatment of animals with any of three regimens of aspirin (0.5 mg/kg/24h: 10 mg/kg/24h: 40 mg/kg/24h) plus dipyridamole (2 mg/kg/6h), or dipyridamole alone failed to prevent early vein graft induced activation of platelets. Autoradiography studies in the treated group followed for eight months (10 mg/kg/24h aspirin plus 2 mg/kg/6h dipyridamole) showed that in contrast to the untreated animals, platelets were still deposited at this time. In addition, platelet deposition was shown to be enhanced in the high dose aspirin plus dipyridamole group at one month compared with the low dose aspirin plus dipyridamole group.

These results suggest that aspirin does not prevent platelet/vein graft interaction in early postoperative months and in high dose may enhance platelet deposition during this time.

Demonstration of beta adrenoceptor blockade by the class I antiarrhythmic agent propafenone hydrochloride

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The postulated beta adrenoceptor blocking properties of the new antiarrhythmic drug propafenone were studied by in vivo comparison against placebo and propranolol in the antagonism of tachycardia induced by exercise and by isoprenaline and by in vitro radioligand binding studies of animal and human left ventricular muscle membrane preparations. Interaction with frog erythrocyte membrane adenylate cyclase was also investigated.

In the clinical studies, a double blind crossover comparison of oral propafenon 300 mg, propranolol 40 mg, and placebo indicated appreciable antagonism of chronotropic response to isoprenaline two hours post dose with dose ratios of 4.1 ± 1.3 (mean \pm SEM) for propafenon and 16.8 ± 5.1 for propranolol. Chronotropic response to exercise was modestly reduced by propafenon. Analysis of the binding of ^{125}I iodocyanopindolol to human left ventricular muscle membranes showed specific beta adrenoceptor competition by propafenon, with an EC_{50} of 111 ± 13 nmol. Propranolol EC_{50} was 2.4 ± 0.2 nmol in this system. Competitive inhibition of isoprenaline stimulated frog erythrocyte membrane adenylate cyclase activity was also obtained with propafenon. The ratio of affinities (calculated from the apparent dissociation constant, K_D) for propranolol:propafenon was 1:40 for the in vivo study and 1:50 for the in vitro system.

Propafenon is a specific antagonist of the human beta adrenoceptor and this action can be shown during in vivo study in human subjects. At clinical dosages it appears likely that it will achieve a modest degree of beta blockade, which may contribute to its antiarrhythmic effect.

Study of the electrophysiological effects of early or subendocardial ischaemia using intracavitary recordings

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The early ionic and electrical changes resulting from myocardial ischaemia are involved in the genesis of malignant ventricular arrhythmias and abnormalities of myocardial contractility. The acquisition of electrophysiological data during early ischaemia in the intact heart is thus of importance.

These studies have evaluated the use of clinically applicable intracavitary recordings of the paced endocardial evoked response and monophasic action potentials as indices of the electrophysiological changes produced by transient regional myocardial ischaemia. The technique has been validated in open chested dog experiments and during cardiac catheterisation studies in man.

Regional ischaemia caused asynchronous activation due to differential conduction delay and produced an abnormal rate corrected shortening of the local repolarisation rate as evaluated by both techniques. These early patterns of change in the duration of the regional repolarisation occurred at subthreshold pacing rates and preceded clinical ischaemia by an average of four minutes.

In the animal experiments verapamil pretreatment altered the rate at which the shortening of repolarisa-

tion and asynchronous activation occurred during ischaemia. The major beneficial effect of nitroglycerin on the electrical changes of ischaemia in man was related to decreased oxygen demand.

Thus intracavitary recordings of the paced endocardial evoked response and monophasic action potentials are a sensitive means of detecting and monitoring the electrophysiological changes of early or subendocardial ischaemia and permit the assessment of pharmacological interventions on the resulting abnormalities in ventricular repolarisation.

Endothelial relaxant factor and coronary arteries: an experimental study

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Using a newly developed isolated buffer-perfused rabbit coronary preparation we showed that vasoconstrictor responses were almost abolished by the presence of endothelium compared with those in endothelially denuded arteries. Local endothelial damage unmasked local constrictor responses ("vasospasm"). Aortic preparations were relatively little affected by this endothelium dependent effect. Furchgott and others have reported endothelium dependent modulation of constriction in many different arteries and species, including man, but its mechanism has remained unknown.

Cascade experiments in which aortas and coronary arteries were perfused in series provided evidence that this endothelium dependent relaxation is due to a humoral agent—endothelial relaxant factor (ERF). ERF could be specifically blocked by a number of agents whose only common property is that they are antioxidants and which included borohydride and thiol reagents. Manipulation of transit time and addition of ERF antagonists at different sites showed that the half life of ERF is 6 s and that the antagonists act by chemically inactivating ERF. The data indicate that ERF is an unstable compound with a carbonyl group and not a lipoxygenase product or free radical as previously suggested. A substance of such ubiquity and potential dilator potency is likely to have considerable physiological and pathophysiological importance.

Failure of exercise testing to predict outcome after transmural and non-transmural myocardial infarction and unstable angina

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Although the immediate outcome after transmural and non-transmural myocardial infarction and unstable angina differs, the value of exercise testing in predicting the long term outcome of each group is not established. Accordingly, 214 consecutive, one month survivors were classified into group A, after transmural infarction ($n=121$); group B, after non-transmural infarction ($n=24$); and group C after an episode of unstable angina ($n=69$). During a 10 month mean follow up the incidence of angina was 21% in group A but 48% in groups B and C ($p<0.01$). Death occurred only in group A (six patients). Heart failure occurred in groups A and B (10 and two patients respectively), and reinfarction in all groups (eight, two, and four patients respectively). The incidence of these events was not significant between groups, although heart failure and death were more common in group A than in groups B and C combined ($p<0.05$). One hundred and forty three patients (67%) performed symptom limited treadmill exercise at one month, while the remaining patients, whose outcome was the same, were not exercised for non-medical reasons. Neither ST segment changes nor an abnormal blood pressure response predicted the patients who subsequently reinfarcted, died, or developed heart failure. Although the long term outcome after transmural and non-transmural infarction and unstable angina was different, exercise testing in any group was not able to predict patients at increased risk.

Reproducibility and diurnal variation of predischARGE submaximal exercise testing after myocardial infarction

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Reproducibility and diurnal variation of a submaximal treadmill exercise test were studied in 41 patients aged 34–66 years, receiving no drugs, a mean of eight days after acute myocardial infarction using a limited Naughton protocol. Each patient was exercised before 8 am and after 6 pm on two consecutive days. Exercise induced parameters analysed were ST segment depression and elevation, angina, ventricular arrhythmias, and exercise duration. Twenty one patients had 84 reproducible tests for all parameters and showed no diurnal variation. Exercise induced ST segment depression occurred in 14 patients but was reproducible in only eight. The six patients with non-reproducible ST segment depression on exercise showed no diurnal pattern and five had subendocardial infarctions. Fourteen patients had exercise induced ST segment elevation, but this was reproducible in all four tests in only 10 patients, the remaining

four showing no diurnal variation. Exercise induced angina was not reproducible in six of the 10 patients in whom it occurred and showed no diurnal pattern. Exercise induced ventricular arrhythmias occurred in eight patients: they were not reproducible, but occurred mainly in the evening test. Four patients had limited exercise duration, and this parameter was reproducible in all four tests for each patient. Only 51% of this group of patients had reproducible predischARGE submaximal exercise tests for all analysed parameters. Patients with subendocardial infarctions showed less reproducibility for symptomatic and objective features of myocardial ischaemia than those with transmural infarctions. None of the analysed parameters showed appreciable diurnal variation.

Critical comparison of early and late exercise stress testing after acute myocardial infarction

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Exercise stress testing after myocardial infarction is now recognised as useful in predicting prognosis, but the precise timing and nature of the tests to be performed remain controversial. We have compared early submaximal Naughton protocol and later maximal Bruce protocol treadmill testing. One hundred and seventy subjects (139 men and 31 women; mean age 54.4 years, range 32–65) underwent submaximal stress testing 10 days (range 5–19) after acute myocardial infarction. One hundred and fifty subjects proceeded to the maximal test 34 days (range 22–56) after the acute event. There were no significant differences between the two tests in the proportions of subjects showing ST depression, ST elevation with Q waves, inadequate blood pressure responses, or angina. Significant ventricular arrhythmias, however, were more common in the maximal test, 13% *v* 3% ($0.001 < p < 0.01$). Twenty patients did not undergo a second test, 11 because of complications. These included four patients who died, three with unstable angina, and one each with recurrent infarction, left ventricular failure, pericarditis, and arrhythmia. These early complications were poorly predicted by treadmill testing, a fall in blood pressure ≥ 20 mmHg from peak or failure to rise being the only, weak, association.

The two exercise tests therefore produced comparable overall results, apart from a divergence in arrhythmias, so that timing and form of the test may not be critical.

Early exercise testing and coronary bypass surgery after infarction

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After an uncomplicated myocardial infarction 114 patients were prospectively studied by maximal treadmill stress testing (MST) and coronary angiography at two and six weeks respectively. At angiography 84 patients had appreciable coronary artery disease in non-infarct areas. In 79 (94%) of these the MST correctly identified the areas of additional myocardial ischaemia. Five patients had a false negative MST for additional disease. Based on the anatomical lesions or symptoms, or both, 53 patients were allocated to undergo surgery. Of these, 47 underwent coronary surgery within three months of myocardial infarction. One patient died perioperatively and 46 are symptom free during a mean follow up period of 23 months. Of the six awaiting surgery one died from reinfarction at four months. Sixty one patients were allocated to receive medical treatment. At angiography 30, 24, and seven patients had one, two, and three vessel coronary artery disease respectively. The MST correctly predicted the anatomy in 57 (93%). The seven patients with three vessel coronary artery disease treated medically had inoperable lesions and at follow up one died from further infarction, four remain symptomatic, and two are asymptomatic. Thus at a follow up period of two years the high risk group with a predicted average mortality of about 20% have a mortality of 2% and our overall mortality is only 3%.

Haemodynamic significance of left ventricular gradient in hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy is characterised by hyperkinetic left ventricular function, but the effect of an outflow tract gradient on the haemodynamics of ejection remains controversial. To determine the percent of stroke volume ejected during early and late systole we performed technetium 99m gated equilibrium radionuclide angiography in 18 normal subjects and 57 patients, 29 with and 28 without left ventricular gradients. Time-activity curves were generated from list-mode data, and the percentage of stroke volume ejected during various phases of systole was computed. The percentage of stroke volume ejected during the initial third, the initial 50%, and the first 80% of systole was greater in patients with hyper-

trophic cardiomyopathy than in normal subjects (54 ± 6 v 45 ± 2 , $p < 0.01$; 70 ± 6 v 65 ± 3 , $p < 0.01$; and 91 ± 4 v 88 ± 1 , $p < 0.01$ respectively), but was identical in patients with and without left ventricular gradients. The duration of systole was similar in the three groups. These findings favour the interpretation that a left ventricular gradient does not represent true obstruction.

Catecholamine release in hypertrophic cardiomyopathy: a comparison with coronary artery disease

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Plasma noradrenaline concentrations were measured by a radio enzyme assay in 29 patients, 18 of whom had coronary artery disease and 11 of whom had angiographically proved hypertrophic cardiomyopathy with normal coronary arteries. Simultaneous coronary sinus and femoral artery measurements were made both at rest and during rapid atrial pacing.

The mean resting arterial noradrenaline concentration in coronary disease was 298 ± 64 pg/ml compared with 513 ± 102 pg/ml in hypertrophic cardiomyopathy; the difference was not significant, nor was a change seen during atrial pacing. Myocardial noradrenaline flux was calculated as (coronary sinus - arterial noradrenaline) \times coronary sinus blood flow \times 1-haematocrit. In patients with coronary disease a change in uptake to release of noradrenaline occurred during atrial pacing (-3321 ± 3663 to $+8250 \pm 6981$ pg/min). A directionally opposite change was seen in patients with hypertrophic cardiomyopathy (-5801 ± 8584 to -33563 ± 14639 pg/min). A comparison of the change in flux from rest to pace between the groups was significant at the 5% level.

These results suggest a difference in noradrenaline metabolism between ischaemic and hypertrophic myocardium, which is independent of change in global coronary blood flow.

Effects of verapamil and A23187 on triac induced myocardial changes in rats. A possible pathogenetic mechanism for hypertrophic cardiomyopathy

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Disarray is regarded as a marker for the morphological diagnostic confirmation of hypertrophic cardiomyopathy. Triac, the acetic acid metabolite of triiodothyronine, produces myocardial disarray and hypertrophy in the offspring of treated rats similar to that seen in man with hypertrophic cardiomyopathy. Clarification of its mode of action may define possible pathogenetic mechanisms for this disease. To investigate the influence of calcium inhibition, 18 pregnant rats were divided into six groups: three received 1-4 mg/day of verapamil, together with 60 µg of triac; one 60 µg of triac alone; one 4 mg of verapamil alone; and a control group 0.6 ml of buffer. The results showed that in the offspring a low dose of verapamil with triac reduced disarray and hypertrophy. Surprisingly, 4 mg of verapamil alone increased hypertrophy. To substantiate the role of calcium the ionophore A23187 was substituted for verapamil, resulting in changes similar to those induced by triac.

It is concluded that triac, which acts on myocardial cell membranes, facilitates the entry of calcium ions, increasing contractility. This prevents normal alignment of myofibrils, resulting in disarray. An endogenous pathogenetic mechanism may be operative in patients with the unusual but important association of hypertrophic cardiomyopathy with covert hyperthyroidism.

Influence of amiodarone on survival in hypertrophic cardiomyopathy

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We have assessed the effect of amiodarone on survival in patients with hypertrophic cardiomyopathy and ventricular tachycardia in an open non-randomised study. Between 1976 and 1977 (before amiodarone was evaluated), 72 hour electrocardiographic examination was performed in 86 consecutive patients; 24 with ventricular tachycardia received conventional antiarrhythmic agents. Seven patients died suddenly during follow up of three years; of these, five had had ventricular tachycardia which was poorly controlled and two had no ventricular tachycardia. From 1977 to 1979, ventricular tachycardia was detected in 21 of the next 82 consecutive patients with hypertrophic cardiomyopathy. Of these, 20 received amiodarone (150-400 mg/day, median 300): ventricular tachycardia was suppressed in all during repeated 48 hour electrocardiographic examination. Three patients died suddenly during a three year follow up, but none was from the amiodarone treated ventricular tachycardia group. Control of ventricular arrhythmia with amiodarone was associated with improved survival ($p < 0.04$). This effective control of ventricular

arrhythmia in patients with hypertrophic cardiomyopathy indicates the value of amiodarone in the prevention of sudden death and that this may also extend to patients without detected ventricular tachycardia.

Cross sectional echocardiography: a real alternative to cardiac catheterisation in coarctation syndrome

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Recent studies have suggested that cross sectional echocardiography in infants with coarctation syndrome could determine both the precise intracardiac and aortic anatomy, thus obviating the need for catheterisation with its attendant risks. To determine whether the advantages of avoiding preoperative catheterisation were outweighed by any morbidity consequent on echocardiographic misdiagnosis, a prospective study was undertaken, in which 21 consecutive infants in cardiac failure were referred for aortic repair based solely on the combined clinical and echocardiographic examination. Echocardiography correctly predicted the aortic anatomy in 20 cases (two aortic interruption, six hypoplastic arches and discrete juxtaductal coarctations, 12 juxtaductal coarctations). In one case aortic interruption was misdiagnosed as long segment arch hypoplasia. Associated intracardiac malformations were consistently predicted (four complex heart disease, 10 ventricular septal defects, one aortic stenosis, one mitral stenosis, one secundum atrial septal defect). Primary repair was successful in 20 cases. One case subsequently required revision of the repair. During the study a further 313 infants underwent echocardiography with no false positive or false negative diagnosis of coarctation.

We conclude that cross sectional echocardiography is an extremely accurate diagnostic technique in identifying infants with coarctation syndrome and, in our experience, has replaced catheterisation before coarctation repair.

Cardiac surgery in infants without prior cardiac catheterisation

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Between June 1981 and July 1983, 52 symptomatic

infants underwent cardiac surgery without prior cardiac catheterisation. In all cases the diagnosis was established from clinical evaluation and from cross sectional echocardiography. There were 19 infants who underwent surgery with the aid of cardiopulmonary bypass, including eight with total anomalous pulmonary venous connection, three with truncus arteriosus, two with cor triatriatum, two with critical pulmonary valve stenosis, and one each with complete atrioventricular septal defect, critical aortic valve stenosis, or large doubly committed subarterial ventricular septal defect. A neonate with complete transposition had anatomic correction. Twelve neonates with severe cyanosis had a modified Blalock-Taussig anastomosis. Pulmonary artery banding was performed on five infants with univentricular atrioventricular connection. Five infants required repair of coarctation and banding of the pulmonary artery. Finally, four infants underwent repair of isolated coarctation and seven had ligation of a ductus arteriosus. Cross sectional echocardiography failed initially to show an aortopulmonary window in an infant with a coexisting large patent ductus and in addition failed to recognise type 2 truncus arteriosus in two cases. The overall mortality in this group was 10%. Avoidance of cardiac catheterisation avoids complications from this procedure and may allow infants to undergo surgery in better conditions, thus reducing the operative risks.

Evaluation of one and two stage anatomical correction of simple transposition of the great arteries

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Between 1975 and 1983, 72 patients underwent anatomical correction of transposition of the great arteries; of these, 38 had simple transposition with intact ventricular septum. The left ventricle was judged to be sufficiently developed to allow one stage correction in 12 patients. This group comprised six neonates aged 10 days to 5 weeks and six infants with dynamic left ventricular outflow obstruction aged 7 to 23 months; the remaining 26 patients had "underdeveloped" left ventricles requiring a first stage operation of banding with or without aortopulmonary shunt two to 11 months before anatomic correction at the age of 4.5 to 21 months. There were no deaths associated with one stage correction and two deaths in the 26 patients undergoing second stage procedure, giving an overall mortality of 5% (2/38). During a follow up of one week to six and a half years there were no late deaths. All patients have been regularly assessed by clinical examination, chest radiograph, 12

lead electrocardiogram, and M mode and two dimensional echocardiography. Fifteen patients underwent routine recatheterisation and angiography one or more years after operation. Appreciable complications included early obstruction of the left coronary artery in one patient (2.5%) and supra valve pulmonary stenosis in two (5%) (which was successfully relieved by operation). It is concluded that anatomical correction is possible in all patients with transposition of the great arteries in the absence of organic left ventricular outflow obstruction and that the need for a first stage procedure is determined by the state of the left ventricle.

Coarctation of the aorta and ventricular septal defect. A morphological study

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Despite adequate relief of the coarctation, there remains an appreciable mortality among infants with associated ventricular septal defect. To elucidate morphological factors which may be important, we studied the detailed anatomy of 43 such hearts.

The interventricular communication was variable both in size and position. It was large in 28 cases, moderate in 12, and small in three. Perimembranous defects extended into the inlet septum (18), trabecular septum (six), and outlet septum (two), while muscular defects occupied the inlet (five) or trabecular (seven) septum. The defects were multiple in five hearts. Associated secundum atrial septal defects were present in 13. Left ventricular inlet anomalies, found in 13, included annular hypoplasia, accessory orifice, leaflet dysplasia, atresia, and supra valvar stenosis of the mitral valve. Obstruction of the left ventricular outflow tract occurred in 10 specimens, due to a muscular bar, fibromuscular tunnel, straddling tricuspid valve, or membranous tags. The aortic valve was bicuspid in 19 hearts and dysplastic in three. Morphometric comparison between 22 hearts in this series and 23 normal hearts showed substantial increases in right ventricular wall thickness, tricuspid and pulmonary valve circumference, and ventricular volume indexes.

These findings emphasise the complexity of intracardiac morphology found with coarctation and ventricular septal defect, only some of which is amenable to surgical correction. Successful management thus requires detailed preoperative investigation and a selective policy regarding primary ventricular septal defect closure.

Lessons from early days of pacing

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Pacing in the United Kingdom started in 1955 with high voltage external stimulators, which still have a place in emergencies. Long term pacing was not possible because of pain induced by the high voltage, but we were encouraged to continue to develop pacing techniques when postmortem studies by Crawford and Davies showed that the commonest cause of complete heart block was relatively isolated disease of the conducting tissue. Low voltage stimulation with epicardial electrodes pioneered by Senning carried in our hands a high mortality in elderly patients and also a high incidence of rejection. Endocardial pacing was therefore adopted, and Sowton showed that patients could increase their stroke volume on exertion with a fixed heart rate. We had problems of septicaemia, particularly if the unit was external with nearby venous entry, and this was usually complicated by bacterial infection of the tricuspid valve necessitating complete withdrawal of the endocardial wire. Competition from fixed rate pacing did not produce ventricular fibrillation. Rejection was not uncommon if a second procedure such as resiting the endocardial wire was performed. A large experience in early days of acute infarction block with its liability to ventricular fibrillation led to some important conclusions. Lignocaine was started as the wire entered the right atrium. Endocardial potentials were measured daily and if low it was safe to use fixed rate pacing. Fast pacing prevented ventricular fibrillation.

It is hoped that highlighting some of the early problems encountered in pacing will help current practice.

Cardiac transplantation: four and a half years' experience

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Fifty two patients underwent cardiac transplantation between January 1979 and 1 July 1983. Ages ranged between 16 and 52 (mean 42) years, and all but three were men. Twenty patients had cardiomyopathies and 29 ischaemic heart disease. During this period 353 patients were referred for transplantation, of whom 183 were assessed in hospital. One hundred and six were accepted as potential recipients, and of these 40 subsequently died while awaiting transplantation.

Donor ages ranged from 16 to 37 (mean 26) years, and donor heart ischaemic time from 96 to 252 (mean 165) minutes. There was one operative death and six

other deaths within 30 days of operation (early mortality 13%). Two immunosuppressive regimens have been used: anti-thymocyte globulin, azathioprine, and steroids for the first 29 patients and cyclosporin A and steroids for the next 23 patients. All surviving patients have had right and left heart catheterisation at annual intervals.

Thirty of the 52 patients are surviving (three year actuarial survival 51%). Of the 16 late deaths, six have been from acute rejection, four from accelerated coronary artery disease, three from infection, and one each from arrhythmia, graft failure, and brain damage. Those patients who have survived beyond six months have had a substantial improvement in health and in measured exercise capacity.

Influence of perioperative myocardial infarction on the late results of myocardial revascularisation

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Between October 1969 and December 1981 129 (13%) patients undergoing myocardial revascularisation sustained perioperative myocardial infarction defined by electrocardiographic criteria. There was no significant difference in the perioperative myocardial infarction rate and number of grafts or cardioplegia (11%) compared with intermittent cross clamping (6.7%). There was a significant difference, however, between the endarterectomy group (17%) and the non-endarterectomy group (9%) ($p < 0.05$). The actuarial survival including operative mortality was 90% at six years for the patients with perioperative myocardial infarction compared with 85% for the overall group. In 98 patients reinvestigated the graft patency to infarct areas was 80% compared with 91% in the non-infarct ($p < 0.05$). Left ventricular ejection fraction measured in 53 patients showed a decrease from 0.69 ± 0.14 preoperatively to 0.67 ± 0.16 postoperatively in patients with a patent graft to infarcted areas (NS) compared with a change from 0.65 ± 0.11 to 0.61 ± 0.18 (NS) in those with an occluded graft. Computerised segmental wall motion analysis showed that in 34 infarcted areas with patent grafts, 27% of segments improved, 44% deteriorated, and 29% were unchanged compared with 18%, 53%, and 29% respectively in 17 areas with occluded grafts. During a mean follow up of 52 months, 72% of the survivors were asymptomatic or improved.

It is concluded that perioperative myocardial infarction does not appear to influence late survival, although it has a slight deleterious effect on symptomatic outcome and segmental wall motion when associated with blocked grafts.

Total repair of annuloaortic ectasia. A consecutive series of 36 patients

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In the early 1970s supracoronary resection of the ascending aorta leaving a rim of the diseased aorta in place and replacement of the aortic valve was performed on nine patients in our department. The late results, however, showed aneurysmal reformation in several cases. Therefore, in 1975 we adopted total repair—that is, replacement of the ascending aorta and aortic valve with a composite graft including implantation of the coronary ostia into the prosthetic tube. This total repair has been performed on 36 patients. The surgical technique differs from the original method of Bentall and DeBono. We excise the aneurysm and dissect the coronary ostia with a small aortic cuff free. No wrapping procedure is performed. The mean age of the patients was 42.2 years (range 10–66). Nine patients had Marfan's syndrome and 27 only the cardiovascular manifestations. There were four emergency operations (one rupture, three dissections) and 32 elective operations (four chronic dissections). In addition to the total repair, reconstruction of the aortic arch was performed in one case, coronary artery bypass grafting in two, and mitral valve replacement in one case. There was no hospital mortality and no anastomotic complications. Routine control angiography has been performed in all cases. In March 1983 the mean follow up time was three years, two months (range three months–7.5 years) and during this period there has been only one late death, which was due to thromboembolism. We consider the results of the so called total repair so satisfactory that we recommend it as routine treatment of annuloaortic ectasia.

Patient status 10 or more years after "fresh" homograft replacement of the aortic valve

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One hundred and forty consecutive patients aged 12–74 (mean 52) years who underwent isolated elective aortic valve replacement using antibiotic sterilised homografts have been followed for 10–13 (mean 11) years. The dominant lesion was stenosis in 96 patients (69%) and regurgitation in 44 patients (31%). There were four (2.9%) early and 48 (34.3%) late deaths. Valve failure occurred in 37 patients (26%), due to degeneration in 30 (21%) and endocarditis in seven (5%). The freedom from valve failure was 89% at five

years and 72% at 10 years; the rate of valve degeneration was 1% per year up to five years, 2% from five to eight years, and 5% from eight to 10 years. The overall survival rate at five and 10 years was 82% and 66% respectively. The survival at five and 10 years of the patients retaining the original homograft, including early and reoperative mortality, was 82% and 64% in patients with previous stenosis, 82% and 59% in patients with previous regurgitation, and 82% and 62% in the whole group. Functional evaluation of the patients who retained their homograft at 10 years showed excellent or good results in 54 patients (72%) and fair or poor in 21 (28%).

It is concluded that homograft replacement of the aortic valve gives satisfactory results for up to 13 years; there is a progressive but slow increase in the rate of valve regeneration, particularly after the eighth year.

Myocardial reoxygenation damage is amenable to therapeutic intervention

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Whether the exacerbation of myocardial damage known to occur with calcium influx on reperfusion/reoxygenation after ischaemia/hypoxia is an inevitable consequence of the preceding insult or whether it is amenable to therapeutic intervention is an important, unresolved question. We used an established model of ouabain treated cat or rabbit papillary muscle preparations and measured the rise in resting tension (contracture) and associated loss of contractile performance which occur on reoxygenation in groups of muscles ($n \geq 6$) treated with different agents at the end of the hypoxic period.

Contracture was significantly reduced at 10 min reoxygenation by $MgCl_2$ (30 mmol), $MnCl_2$ (8 mmol), metabolic acidosis (pH 6.5), and diltiazem (10^{-4} mol), but not by verapamil (10^{-4} mol) or lidoflazine (2×10^{-5} mol), which are more negatively inotropic than diltiazem. In all cases contracture and contractile failure still occurred. Contracture could be prevented by removing Ca^{++} , but its subsequent replacement, essential for recovery, caused severe contracture and contractile failure ("calcium paradox"). Reduction of Ca^{++} concentration to 0.125 mmol and gradual replacement over 60 min to 2.5 mmol prevented contracture and led to full contractile recovery. These findings show that it is possible to prevent myocardial reoxygenation damage and suggest that diltiazem may prevent calcium influx other than by slow channel blockade.

Myocardial potassium loss during tachycardia, pacing induced ischaemia, and coronary occlusion in man

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Ischaemia causes accumulation of extracellular potassium in myocardial tissue. Using catheter-tip ion-selective electrodes, we have investigated this process in man by continuously recording coronary sinus potassium concentration during atrial pacing and percutaneous transluminal coronary angioplasty. Incremental atrial pacing in 10 patients with coronary artery disease caused chest pain and ST segment depression on a 12 lead electrocardiogram. Coronary sinus potassium concentration rose continuously during the test, reaching 0.38 ± 0.03 mmol/l above control. Arterial potassium concentration did not change. Nine patients (including five with normal coronary arteries) remained symptom free during atrial pacing with no electrocardiographic changes. Their coronary sinus potassium concentration rose by 0.19 ± 0.04 mmol/l before declining to 0.07 ± 0.02 mmol/l above control by the end of the test ($p < 0.001$ between groups). Coronary sinus potassium concentration was recorded in five patients undergoing percutaneous transluminal coronary angioplasty of stenoses in the left anterior descending coronary artery. Little change in coronary sinus potassium concentration was observed during arterial occlusion ($n = 22$). After balloon deflation a transient rise in coronary sinus potassium concentration (range 0.2 to 1.55 mmol/l) was observed when occlusion time had exceeded 15 s ($n = 20$). Of these, only four occlusions were accompanied by chest pain, electrocardiographic change, or increase in heart rate. Continuous recording of coronary sinus potassium concentration shows that ischaemic myocardial potassium loss occurs within 20 s of the onset of ischaemia and precedes chest pain. This loss can be distinguished from that associated with increase of heart rate.

Frequency of changes in perfusion during spontaneous ischaemia in anginal patients

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Patients with coronary disease may suffer silent infarction and sudden death, and ambulatory electrocardiographic evidence of asymptomatic ST depres-

sion suggests silent and spontaneous ischaemia. In 109 patients with angina pectoris and coronary disease, positron tomography was used to measure regional myocardial uptake of rubidium-82 (flow \times extraction) before, during, and after a standard supine exercise. In 19/109 patients 22 episodes of spontaneous ischaemia were identified with tomography. During spontaneous episodes 9/22 were associated with pain and 9/22 were associated with ST change. For these events the control regional myocardial uptake of rubidium-82 was 0.49 ± 0.06 (mean \pm SD), CV = 9.27% (mean coefficient of variance for seven regions of interest). During the events regional myocardial uptake of rubidium-82 increased in normal areas to 0.54 ± 0.1 while abnormal areas decreased to 0.41 ± 0.08 , overall CV = 17.49%. Eight spontaneous episodes were resolved with nitrates. In the same 19 patients before exercise the regional myocardial uptake of rubidium-82 was 0.47 ± 0.06 , CV = 10.46%. During exercise normal areas increased to 0.58 ± 0.09 while abnormal areas decreased to 0.40 ± 0.08 , overall CV = 17.49%. Spontaneous ischaemia occurred in the same region as exercise in all cases. In these patients spontaneous ischaemia was not infrequent and was often silent. These events may be important in the morbidity suffered by patients with coronary disease.

Phase distortion in electrocardiographs—a potential source of serious errors

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Electrocardiographs incorporate filtering which reduces unwanted noise but may distort the recording. The amplitude response of such filters follows the American Heart Association specification, but phase response is unspecified. We have documented six cases where electrocardiographs with inadequate phase response produced ST segment distortion, leading to incorrect diagnoses of acute myocardial infarction.

To investigate the effect of a non-linear phase response on the electrocardiogram a standard electrocardiograph was modified to permit alterations in phase response independently from amplitude characteristics. The modified machine still met current standards. When phase non-linearity was increased, low frequency components of the QRS complex were delayed and distorted the ST segment, mimicking myocardial ischaemia. The magnitude of the distortion depended on signal morphology.

We also measured the phase and amplitude responses of three electrocardiographs and three ambulatory recorders. Waveform distortion occurred

in those machines with a non-linear phase response. Correction of the phase response minimised the distortion.

Filters can be designed to reduce baseline drift more effectively than those permitted under the current standard, but phase response is as important as amplitude response. Both should be specified in a new standard for electrocardiographs.

Paediatric use of disopyramide

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Disopyramide is prescribed to adults in a dose of about 6 mg/kg/day and has an effective plasma concentration in the range 2–5 mg/l. We have studied the relation between age, dose, plasma concentration, and clinical efficacy of disopyramide in a group of paediatric patients. Fifteen patients, aged 2 weeks to 14 years, received oral disopyramide for ventricular or supraventricular arrhythmias. In six cases there was no predisposing cause; the remainder had congenital heart malformations (three), cardiomyopathy (four), or conducting tissue abnormalities (two). Predose plasma disopyramide concentrations were measured after at least 48 hours' treatment. Initial dosage, 3–6 mg/kg/day, was adjusted to achieve a plasma disopyramide concentration of 2 mg/l. Seven patients responded to disopyramide: mean \pm SD plasma disopyramide concentration was 2.39 ± 0.89 mg/l (71 observations). Eight patients did not respond, being transferred to other treatment after dosage adjustment to achieve mean plasma disopyramide concentration of 2.30 ± 0.96 mg/l (14 observations). No symptoms or signs of toxicity were noted. Overall, there was an inverse relation between age and the dose needed to achieve a plasma disopyramide concentration of 2 mg/l, up to 35 mg/kg/day being required, but the spread of results was wide.

It is concluded that (1) high doses of disopyramide may be needed by paediatric patients to achieve effective concentrations, (2) these doses are not associated with adverse effects, and (3) plasma measurements guard against the premature termination of treatment.

Three eras of paediatric pacing

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Between 1976 and 1983, 30 children received permanent pacemakers. Eight were aged under 5 years, 14 were aged 5–13, and eight were aged 13–17.

Indications for permanent pacing were complete atrioventricular block (14), sick sinus syndrome (10), second degree heart block (four), re-entry supraventricular tachycardia (one), and ventricular tachycardia (one); 16 had associated congenital heart disease and two cardiomyopathy. The cardiac arrhythmia was the only abnormality in 12. Before 1977 epicardial leads with non-programmable pacemakers were used in three older children (aged 13–17) without complication or the need to revise the pacemaker system to allow for growth. Between 1977 and 1982, 11 children had epicardial pacemaker systems while nine received transvenous systems using active fixation (seven helifix, two tined). Fifteen received programmable units (Siemens Elema 668 (eight), Cordis 337A (two), 334A (two), 340A (two) and 208A (one)), enabling adjustment of the heart rate in 11 and the output in three, so avoiding reoperation. Lead follow up experience for this era was 330 months for endocardial and 352 months for epicardial leads. One lead displacement occurred (within one hour of endocardial implantation); two deaths occurred (severe structural heart disease (one), unrelated (one)).

Two of the four implantations that were complicated by infection were epicardial and required exploration by thoracotomy. Three epicardial leads fractured. Since 1982 six children (aged 4–9) have received a combination of the smallest endocardial lead (6F Helifix) with the smallest multiprogrammable pacemaker (Cordis 340A). One child (aged 12) received a dual chamber system for re-entry tachycardia. There have been no complications in the latest era of children's pacing using small versatile transvenous systems.

Doppler ultrasound as an alternative to contrast echocardiography

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M mode and real time echocardiography can be augmented by the injection of physiological solutions to produce "contrast echo" studies as a method of delineating blood flow. Blood flow can also be detected by the more recent technique of pulsed Doppler ultrasound done as a simultaneous technique with real time imaging and not requiring any contrast injections. This method has been evaluated in 62 children with either atrial or ventricular defects. In the 28 patients with atrial defects the flow across the atrial septum was detected, directionally, showing the direction of flow in systole and diastole and with the variations superimposed by respiration. In the 31 patients with ventricular septal defects (confirmed by

angiography) the site of the defect was detected by the Doppler in all. Four patients (not studied by angiography) thought clinically to have either a small ventricular septal defect or trivial mitral regurgitation were shown by the Doppler to have no flow across the septum but to have mild mitral regurgitation.

The ability to detect the presence of and direction of abnormal blood flow within the heart non-invasively greatly compliments real time imaging, particularly when recourse to contrast injections is not necessary, and the technique can be applied simultaneously with an imaging study.

Digital subtraction angiography in congenital heart disease

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Selective single plane digital subtraction angiography

was used as an alternative to conventional biplane cineangiography during cardiac catheterisation in 60 children with congenital heart disease. The age of the patients ranged from 13 hours to 12 years. Using radiographic contrast medium diluted to half standard concentration and delivered in bolus volumes comparable to that used in conventional cineangiography satisfactory diagnostic information was obtained in all patients. The dynamic images, though less sharp than cine film, offered better contrast, and no patient required a confirmatory study using cine film. In each case the accumulated doses of radiographic contrast medium and radiation exposure were lower than in a comparable group of patients investigated using conventional cineangiography.

We conclude that single plane digital subtraction angiography is a viable alternative to conventional biplane cineangiography for the investigation of congenital heart disease with the additional advantage of an appreciable saving in both capital expenditure and running costs.